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DERWENT-WEEK: 200027

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TITLE: Prolonged release ophthalmic composition for
human and veterinary use comprises active agent in gel-
forming aqueous vehicle

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PATENT-ASSIGNEE: LEO PHARM PROD LTD[LOVE]

PRIORITY-DATA: 1998DK-000864 (June 30, 1998)

PATENT-FAMILY:

| PUB-NO | PUB-DATE | LANGUAGE |
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| WO 0001365 A1 | January 13, 2000 | EN |
| AU 9946023 A | January 24, 2000 | EN |

DESIGNATED-STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK
EE ES FI
GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU
LV MD MG
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| CIPS | A61K31/496 | 20060101 |
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ABSTRACTED-PUB-NO: WO 0001365 A1

BASIC-ABSTRACT:

NOVELTY - Prolonged release ophthalmic composition for human and veterinary use containing fluoroquinolones or their salts are new.

DESCRIPTION - Prolonged release ophthalmic composition for human and veterinary use comprises a fluoroquinolone compound or its derivative or salt, dispersed in a gel-forming aqueous vehicle.

INDEPENDENT CLAIMS are also included for the following:

(a) a method for preparing the above composition comprising dispersing the active substance in the gel-forming aqueous vehicle; and

(b) a method of administering the active or prophylactic substance to the mammalian eye by applying the composition to the fornix inferior.

None given.

USE - Compositions are useful in the treatment or prevention of eye infections or inflammation of the eye.

ADVANTAGE - Ophthalmic compositions comprising fluoroquinolones need last longer in situ, need fewer applications per day and increase patient compliance. The amount of composition (A) in rabbit lachrymal fluid was compared with commercially available ophthalmic preparations of Zoroxin and Exocin following a single dose. The conventional preparations produced effective concentrations in the lachrymal fluid for 5-6 hours. The new composition achieved an effective concentration for 24 hours.

EQUIVALENT-ABSTRACTS:

PHARMACEUTICALS

Preferred Composition: The fluoroquinolone is ofloxacin, ciprofloxacin, norfloxacin, lomefloxin, enoxacin, premafloxin, fleroxacin,

prulifloxin or preferably
6-fluoro-1-methyl-4-oxo-7(1-piperazinyl)-4H-(1,3)-thiazeto(3,2-a)-quinolin-3-carboxylic acid NM394. The solubility of the active substance is 0.1-0.3 mg/ml in isotonic phosphate buffer at pH 7-7.4 at 32-34 degrees C, or in water at room temperature. The gel-forming vehicle is preferably a mucoadhesive, polyacrylic acid polymer cross-linked with polyalkenyl ethers or divinyl glycol, preferably wt.% Carbopol 974P (0.1-5, preferably 0.5). The composition is pH 6-8.5 and adjusted to give an active substance solubility of no more than 0.2 mg/ml. The pH is also such that the mucoadherent properties of the gel give a suitable concentration of the drug in the lachrymal fluid for at least 6 hours (as determined by a rabbit eye test). The viscosity of the gel is 20-3000 (preferably 1500-2500) mPa at 20 degrees C with a shear rate of 100 second⁻¹. The composition optionally comprises an excipient. Adding normal saline (1 ml) results in a visible out-salting precipitation of the polyacrylic polymer.

Preparation: The composition is prepared by:

- (1) suspending the active substance in an aqueous medium and optionally adding a suitable excipient;
- (2) sterilizing the suspension;
- (3) milling to the desired particle size;
- (4) dispersing polyacrylic acid polymer in an aqueous medium optionally comprising an excipient to form a dispersion;
- (5) adjusting the pH to 6-8.5 (preferably 7.4) then optionally sterilizing the dispersion; and
- (6) adding the suspension to the aqueous gel forming vehicle.

Applied topically to the inferior fornix of the eye. No dosage specified.

SPECIFIC COMPOUNDS

6-Fluoro-1-methyl-4-oxo-7(1-piperazinyl)-4H-(1,3)-thiazeto(3,2-a)-quinolin-3-carboxylic acid NM394, 8 other fluoroquinolones and Carbopol 974P polyacrylic acid polymer are specifically claimed.

Composition (A) comprised NM 394 (3 mg), Carbopol (5 mg), Glycerol 85 % Ph.

Eur (22 mg), benzalkonium chloride (0.05 mg), 5 N sodium hydroxide titrated to pH 7-8, and water for injection to make 1 ml.

TITLE-TERMS: PROLONG RELEASE OPHTHALMIC COMPOSITION HUMAN VETERINARY COMPRISE

ACTIVE AGENT GEL FORMING AQUEOUS VEHICLE

DERWENT-CLASS: A96 B02 C02

CPI-CODES: A12-V; A12-V01; B04-C03; B06-D02; B06-E05; B06-F05; B14-A01;

B14-C03; B14-N03; C04-C03; C06-D02; C06-E05; C06-F05; C14-A01;

C14-C03; C14-N03;

CHEMICAL-CODES:

Chemical Indexing M1 *08*

Fragmentation Code

M421 M423 M431 M782 N104 P220 P420 P922 R023

Specific Compounds

RA00I9

Registry Numbers

184613

Chemical Indexing M2 *01*

Fragmentation Code

D011 D013 D023 E520 F011 F014 F553 H1 H141 H181

H2 H202 H6 H601 H641 J0 J011 J1 J111 J5

J521 M210 M211 M240 M273 M281 M320 M412 M431 M511

M521 M530 M540 M782 M800 N104 P220 P420 P922 R023

Ring Index Numbers

03279

Specific Compounds

R04552 R11676

Registry Numbers

28954

Chemical Indexing M2 *02*

Fragmentation Code

D014 D023 D622 F011 F553 G030 G530 H1 H141 H161
H2 H202 H6 H601 H641 J0 J011 J1 J111 J5
J521 M280 M320 M412 M431 M511 M521 M530 M541 M782
N104 P220 P420 P922 R023

Specific Compounds

R10124

Registry Numbers

91082

Chemical Indexing M2 *03*

Fragmentation Code

D014 D023 D622 F011 F553 H1 H141 H181 H2 H202
H6 H601 H641 J5 J521 M210 M212 M273 M281 M320
M412 M431 M511 M521 M530 M540 M782 N104 P220 P420
P922 R023

Specific Compounds

R04550

Registry Numbers

102303

Chemical Indexing M2 *04*

Fragmentation Code

D014 D024 D622 F011 F013 F553 H1 H141 H181 H2
H202 H6 H601 H608 H642 J0 J011 J1 J111 J5
J521 M210 M211 M212 M240 M273 M281 M320 M412 M431
M511 M521 M530 M540 M782 N104 P220 P420 P922 R023

Specific Compounds

R11682 R11683

Registry Numbers

99570

Chemical Indexing M2 *05*

Fragmentation Code

D014 D024 D622 F011 F014 F553 H1 H141 H182 H2
H203 H6 H601 H609 H642 H681 J0 J011 J1 J111
J5 J521 M210 M211 M273 M281 M312 M321 M332 M342
M362 M391 M412 M431 M511 M521 M530 M540 M782 N104
P220 P420 P922 R023

Specific Compounds

R18337

Registry Numbers

95245

Chemical Indexing M2 *06*

Fragmentation Code

D011 D013 D023 E810 F011 F012 F014 F015 F019 F140
F553 H1 H141 H181 H2 H202 H6 H601 H641 J0
J011 J1 J111 J5 J522 L9 L922 M210 M211 M240

M282 M311 M321 M342 M373 M391 M412 M431 M511 M522
M530 M540 M782 N104 P220 P420 P922 R023
Ring Index Numbers
56713
Specific Compounds
RA1AT4
Registry Numbers
102172

Chemical Indexing M2 *07*

Fragmentation Code
D012 D013 D023 E810 F011 F552 H1 H141 H2 H201
H6 H601 H641 J0 J011 J1 J111 J5 J521 M210
M211 M240 M281 M320 M412 M431 M511 M521 M530 M540
M782 N104 P220 P420 P922 R023
Ring Index Numbers
08400
Specific Compounds
RA1ATA
Registry Numbers
262124

ENHANCED-POLYMER-INDEXING:

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| (21) International Application Number: PCT/DK99/00348 (22) International Filing Date: 23 June 1999 (23.06.99) (30) Priority Data: PA 1998 00864 30 June 1998 (30.06.98) DK (71) Applicant (for all designated States except US): LEO PHARMACEUTICAL PRODUCTS LTD. A/S (LØVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB) [DK/DK]; Industriparken 55, DK-2750 Ballerup (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): DIDRIKSEN, Erik [DK/DK]; Fuglehavevej 14, DK-2750 Ballerup (DK). REFER, Pia, Klic [DK/DK]; Montebello Alle 27, DK-3000 Helsingør (DK). (74) Agent: LARSEN, Marianne, S.; Leo Pharmaceutical Products Ltd. a/s, Patent Department, Industriparken 55, DK-2750 Ballerup (DK). | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |
| (54) Title: PROLONGED RELEASE OPHTHALMIC COMPOSITIONS CONTAINING A FLUOROQUINOLONE (57) Abstract <p>The present invention relates to a pharmaceutical prolonged release ophthalmic composition for human and veterinary use comprising as a therapeutically and/or prophylactically active substance a fluoroquinolone, a fluoroquinolone derivative or a pharmaceutically acceptable salt thereof dispersed in a gel-forming aqueous vehicle.</p> | | |

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PROLONGED RELEASE OPHTHALMIC COMPOSITIONS CONTAINING A FLUOROQUINOLONE

5 The present invention relates to a pharmaceutical prolonged release ophthalmic composition for human and veterinary use comprising as a therapeutically and/or prophylactically active substance a fluoroquinolone, a fluoroquinolone derivative or a pharmaceutically acceptable salt thereof dispersed in a gel-forming aqueous vehicle.

10 BACKGROUND OF THE INVENTION

One of the major problems associated with topical ophthalmic therapy is to maintain an adequate concentration, i.e. a therapeutically and/or prophylactically effective concentration of an ophthalmic drug substance at the desired site of
15 action and within a desired period of time. Furthermore, only a small volume of a composition containing the drug substance can be contained in the *fornix inferior* of an eye, i.e. at the application site, and the composition applied tends to be diluted by the tears or lacrymal fluid and to be drained through the nasolacrymal duct. In order to maintain a sufficient concentration of the drug
20 substance in the eye, traditional ophthalmic compositions are to be applied very frequently such as 5-6 times daily which is very inconvenient for a patient and which leads to problems related to patient compliance.

In recent years, research has been ongoing in the field of developing ophthalmic
25 compositions having a prolonged action, i.e. compositions which may be applied less frequently than the traditional compositions.

It is well known that the duration of action of cationic ophthalmic drug substances may be increased by incorporating such drug substances into gels
30 based on polyanionic polymers, cf. DE-OS 2902863, R.D. Schoenwald et al.: Influence of high-viscosity vehicles on miotic effect of pilocarpine, J. Pharm. Sci., Vol. 14, No. 2 1979, 39-43, and Engelbert Graf et al: Interaction of

Carbopol® 934, with diphenhydramine and dexchlorpheniramine, Acta Pharmaceutica Technologica, 29 (3), 1983, 209-215.

In these compositions the cationic drug substance has formed a salt with the polyanionic polymeric substance and this salt has improved properties with respect to duration of action compared with the plain cationic drug substance. The gel compositions containing the polymeric salt of the cationic drug substance exhibit a duration of action which is about twice that of a conventional ophthalmic drug composition.

Similarly, GB-A-2 013 084 discloses an aqueous gel for treating eye diseases. The composition is a well-retained gel preparation with long-term action containing an ophthalmic drug substance. The ophthalmic drug is reacted with a polymer to provide a complex and/or a salt suitable for topical application. Thus, the ophthalmic drug substance is a cationic drug substance such as pilocarpine. The gel-forming agent is a high-molecular weight polymer having carboxylic or anhydride functional groups and is used in gel compositions at a level from about 2 to about 8% by weight.

EP-B-0 211 020 describes ophthalmic compositions of fusidic acid. A carboxyvinyl polymer has been employed and the pH of the compositions is about 5.8, i.e. at a value where the mucoadhesive properties of the polymer are pronounced.

DESCRIPTION OF THE INVENTION

It has now been found that prolonged release ophthalmic compositions for human and veterinary use comprising as a therapeutically and/or prophylactically active substance a fluoroquinolone, a fluoroquinolone derivative or a pharmaceutically acceptable salt thereof, can be obtained. In contrast to the above-mentioned cationic drug substances, the active substances relevant in the present context are not cationic substances at a pH of about 6.5-8.5, i.e. the above-mentioned principle based on an interaction of a positively charged drug

substance and a negatively charged polymeric substance is not expected to be a proper approach in order to obtain a prolonged release composition containing a fluoroquinolone.

5 Furthermore, the present inventors have observed an amorphous precipitation of NM394 (6-fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4H-[1,3]-thiazeto[3,2-a]-quinoline-3-carboxylic acid), a typical substance for the fluoroquinolone class of substances, when combined with a polyanionic polymer under conditions where salt or complex formation is likely to take place. Thus, the formulation of a
10 prolonged release ophthalmic composition for the fluoroquinolone class of substances is not merely a routine matter for a person skilled in the art.

Formulation of suitable ophthalmic compositions for human and veterinary compositions is a complex matter within the pharmaceutical field due to
15 restricted requirements such as, e.g.,

- i) the composition must not have an irritative effect on the eye,
- ii) the composition may not lead to a blurred vision after application to the eye,
- iii) the elimination by tear turnover should be avoided or reduced, if possible,
- 20 iv) the drug substance should be bio-available (e.g. the drug substance should be able to diffuse through the cornea).

Thus, in general many considerations are involved in the formulation of ophthalmic compositions and often the result obtained, i.e. the composition
25 obtained, reflects a proper balance between the requirements mentioned above.

Especially with respect to ophthalmic compositions it has proved suitable to employ a mucoadhesive substance in the compositions in order to enable a bioadhesion of the composition to the ocular mucosa. Suitable mucoadhesive
30 substances for pharmaceutical use are known, e.g. within the Carbopol® series from BFGoodrich. The Carbopol® polymers are also gel-forming substances. The swelling and the bioadhesiveness of the polymers are dependent on pH (pKa for the Carbopol® polymers is about 6.0), but as the swelling increases with

increasing pH, the bioadhesiveness tends to decrease with increasing pH. When formulating ophthalmic compositions wherein polymers like a Carbopol® is included as a gel-forming substance as well as a mucoadhesive substance, pH of the composition is to be adjusted to an optimal value. The optimal value with respect to bioadhesion is at an acidic pH (pH 5.0 or less).

Surprisingly, suitable ophthalmic compositions have now been developed containing as an active substance a fluoroquinolone substance and releasing the active substance from the composition in such a manner that a therapeutically and/or prophylactically effective concentration in the lacrymal fluid of the eye for at least about 6 hours such as, e.g. about 6.5 hours, 7 hours, 7.5 hours, 8 hours, 9, 10, 11 or 12 hours is obtained. The effect is assessable in the rabbit eye test described in the experimental section herein. The compositions according to the invention have a pH at about neutral and even when the compositions contain a Carbopol® polymeric substance as a gel-forming agent (i.e. in such cases a pH about neutral is not envisaged to be suitable in order to balance swelling and mucoadhesive properties) a prolonged duration of action has been obtainable.

In animal experiments, such compositions have proved suitable for administration to the eye only once or twice daily, in contrast to conventional compositions which are designed to be administered 5-6 times daily.

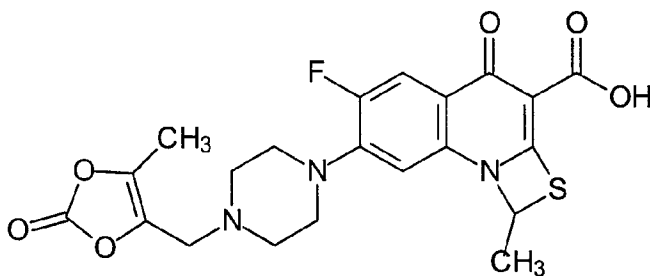
Furthermore, the efficiency of a composition according to the invention is evidenced by the fact that the duration of action is prolonged such that about 10 times as high amounts (of fluoroquinolone) are present in the lacrymal fluid after at least 6 hours compared to the marketed eye drop compositions based on fluoroquinolones such as norfloxacin and ofloxacin, respectively, cf. the examples herein.

A composition according to the invention is useful in the treatment and/or prophylaxis of eye diseases especially eye infections and/or inflammatory conditions of the eye.

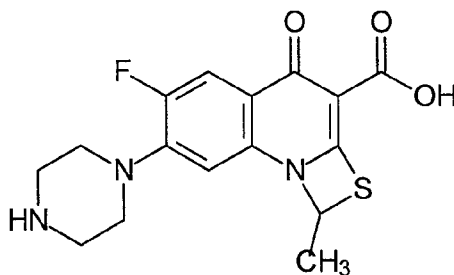
Active substances

5 As mentioned above, a composition according to the invention comprises an active substance. The active substance is a fluoroquinolone, a fluoroquinolone derivative or a pharmaceutically acceptable salt thereof. Preferably, the fluoroquinolone is selected from the group consisting of: ofloxacin, ciprofloxacin, norfloxacin, lomefloxacin, enoxacin, premafloxacin, fleroxacin, 10 prulifloxacin and 6-fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4H-[1,3]-thiazeto[3,2-a]-quinoline-3-carboxylic acid (NM 394).

Notably, NM394, an active principle of prulifloxacin, is of interest in the present context.



Prulifloxacin



NM-394

Fluoroquinolones are synthetic, broad-spectrum, bactericidal drugs particularly active *in vitro* against Gram-negative bacteria. Although their spectra of activity are broadly similar, *in vitro* comparisons have suggested that e.g. ciprofloxacin is more active than ofloxacin against *Pseudomonas aeruginosa* (a cause of severe corneal ulceration), whereas ofloxacin is more active than ciprofloxacin against *Chlamydia trachomatis*. Prulifloxacin (NM441) is a fluoroquinolone antibacterial prodrug of the active principle NM394, which shows potent and broad-spectrum antibacterial activity both *in vitro* and *in vivo*. NM394's activity against Gram-negative bacteria has been found to be comparable to that of ofloxacin and ciprofloxacin, while its activity against Gram-negative bacteria has been found to be equal to that of ciprofloxacin. NM394 has also been found to show superior activity against strains of *Enterobacteriaceae* and *Pseudomonas aeruginosa*. NM394 was found to be as active as ciprofloxacin against anaerobic bacteria inhibiting most strains, but showed weak activity against *Clostridium* spp. and some of the *Bacterioides fragilis* group organisms.

To the best of our knowledge NM394 has never before been formulated as a composition for ophthalmic use. Its prodrug, prulifloxacin, has been administered orally in clinical studies relating to e.g. external eye diseases but no studies have revealed whether prulifloxacin would have any beneficial effect on eye infections when administered directly to the eye. Prulifloxacin administered locally to the eye should be converted to the active principle NM394 by enzymes present in the eye.

In order to improve the duration of action, the active substances should preferably be present in a composition according to the invention in the form of solid particles and, furthermore, the active substance should not dissolve rapidly in the lacrymal fluid upon application but rather be maintained at the application site. The presence of the active substance in the form of solid particles in the eye may reduce the elimination from the eye in that the solid particles are deposited in the *fornix inferior* and are not easily eliminated due to the effect arising from an increase in blinking and lacrimation (which normally leads to a rapid loss of dissolved substances). At the same time, the active substance

should preferably also be in the form of solid particles in the composition. If the active substance is dissolved in the composition, the active substance would – after application to the eye – in an uncontrollable manner precipitate in the lacrymal fluid (due to the low solubility in the lacrymal fluid) and thus lead to e.g. an inappropriate particle size which may give rise to discomfort and pain and poor patient acceptance. Thus, a low solubility of the active substances in the lacrymal fluid as well as in a composition according to the invention is important. The low solubility in the lacrymal fluid has two purposes; to avoid elimination from the eye due to an increase in blinking and lacrimation, and to make use of a relatively slow dissolution of the active substance in order to control the availability of the active substance to the eye (in general, it is contemplated that only dissolved drug substances are able to exert their therapeutically or prophylactical effect) and, accordingly, control the duration of action.

Fluoroquinolones as a class are fairly insoluble in water. All modern fluoroquinolones are zwitterionic in character due to the presence of both a carboxylic acid and a basic amine; pK_a values for these functional groups have been reported to be in the range of from 5.5 to 6.3 for the carboxylic acid and in the range of from 8.6 to 9.3 for the distal amino group. At low pH both the amine and the carboxylic acid are protonated, giving the molecule an overall positive charge. Conversely, at high pH, the amine is in the free base form, while the carboxylic group exists as the carboxylate anion providing a net negative charge. Because of this, fluoroquinolones tend to be more soluble in water at acidic pH and at basic pH with a minimum solubility expressed at neutral (physiological) pH values (cf. "The Quinolones", 2nd Ed. by Vincent T. Andriole, Yale School of Medicine, Chapter 2, Chemistry and Mechanism of the Quinolone Antibacterials).

Specific pK_a values for fluoroquinolones are: Ciprofloxacin: pK_{a1} about 6.1 and pK_{a2} about 8.7, Norfloxacin: pK_{a1} about 6.4 and pK_{a2} about 8.5, Lomefloxacin: pK_{a1} about 5.6 and pK_{a2} about 9.0, Enoxacin: pK_{a1} about 6.2 and pK_{a2} about

8.8, Prulifloxacin: pK_{a1} about 6.1 and NM394: pK_{a1} about 5.9 and pK_{a2} about 8.8.

5 In accordance with the above, the solubility of the active substance is at the most about 0.3 mg/ml such as e.g. about 0.25 mg/ml, about 0.2 mg/ml, about 0.15 mg/ml, about 0.125 mg/ml or about 0.1 mg/ml as determined in isotonic phosphate buffer at a pH of 7.0-7.4 and at a temperature of 32-34 °C. This medium is a suitable aqueous medium to simulate lacrymal fluid under physiological conditions. Furthermore, the solubility of the active substance in
10 the composition is at the most about 0.3 mg/ml such as e.g. about 0.25 mg/ml, about 0.2 mg/ml, about 0.15 mg/ml, about 0.125 mg/ml or about 0.1 mg/ml at room temperature.

15 In order to avoid discomfort of the patient after administration of a composition according to the invention, the particle size of the active substance in a composition should be rather small and fulfil the requirements given in official monographs like Ph. Eur. 3rd Edition, 1997. The method is described in the Experimental section herein. In short, the majority of the particles should have a particle size of less than 25 μm . In practice, the majority of the particles have a
20 size of less than 10 μm such as in a range of about 2-5 μm .

In one embodiment of the invention, a preferred compound is NM394 or a pharmaceutically acceptable salt thereof.

25 The concentration of the active substance in the composition depends on the specific fluoroquinolone employed but is generally sufficiently high to obtain a prophylactically and/or therapeutically effective concentration in the eye after administration. As an example, the concentration of NM394 in a composition of the invention is within a range of from about 0.5 to about 15 mg/ml such as,
30 e.g. from about 1 to about 10 mg/ml, from about 1.5 to about 8 mg/ml, from about 1.75 to about 6 mg/ml, from about 2 to about 5 mg/ml. from about 2.5 to about 4 mg/ml such as, e.g., from about 2.7 to about 3.3 mg/ml. These concentration ranges are relevant for fluoroquinolones in general. If a

pharmaceutically acceptable salt (or derivative) is employed, then the concentration of the salt (or derivative) in the composition corresponds – when calculated on the fluoroquinolone – to the ranges as given above.

- 5 In general, a prophylactically and/or therapeutically effective concentration is determined as the minimum inhibitory concentration (MIC) values in standard assays well known to a person skilled in the art. MIC values for fluoroquinolones are mostly below 1 µg/ml for sensitive microorganisms.

10 Gel-forming agents

- As mentioned above, a composition according to the invention comprises a gel-forming aqueous vehicle. A vehicle suitable for use in the present context comprises an ophthalmically acceptable cross-linked polyacrylic acid polymer. A preferred polyacrylic acid polymer is cross-linked with polyalkenyl ethers or divinyl glycol. Moreover, suitable cross-linked polyacrylic acid polymers are mucoadhesive, cf. Bulletin 16 of BFGoodrich.
- 15

- Examples of preferred polymers for use in a composition according to the invention are carbomers, i.e. homopolymers of acrylic acid cross-linked with an allyl ether of pentaerythritol or an allyl ether of sucrose. Specific examples are carbomers of the series Acrisint® (manufactured by 3V-Sigma), Carbopol® (manufactured by BFGoodrich), PerForMax® (manufactured by BFGoodrich), Synthalen® (manufactured by 3V-Sigma) and Thixol® (manufactured by Mearl).
- 20
- 25 Noveon® polycarbophils from BFGoodrich are also suitable polyacrylic acid polymers.

- Especially, the series of Carbopol® resins (Carbopol® resins having the type Nos. 910, 934, 940, 941, 951, 954, 971, 980, 981, 934P, 974P, 5984 and 1382) have suitable properties for ophthalmic use and Carbopol® 974P is a specific example of a suitable polymer especially because this polymer is being manufactured without the use of benzene in the process. The Carbopol® series of polymers have suitable properties with respect to i) swelling ability and ii)
- 30

mucoadhesive properties. Furthermore, Carbopol® has proved to be a suitable agent for topical application to the eye. It is substantially non-irritative and only to a minor extent a blurred vision is observed upon administration of a composition containing Carbopol®.

5

The concentration of the polyacrylic acid polymer in a composition according to the invention is in a range of from about 0.1 to about 5% w/v such as, e.g. from about 0.1 to about 4% w/v, from about 0.2 to about 3% w/v, from about 0.2 to about 2% w/v, from about 0.2 to about 1.5% w/v or from about 0.3 to about 1.0% such as, e.g., about 0.5% w/v.

10

As mentioned above, the pH of the composition is a very important factor *inter alia* with respect to the following:

15

- i) solubility of the active substance in the composition,
- ii) adjustment of the solubility of the active substance in the lacrymal fluid (e.g. by use of buffer substances in the composition),
- iii) formation of a gel (swelling of the polymer),
- iv) maintenance of the mucoadhesive properties of the polyacrylic acid polymers,
- v) interaction of the active substance with the polyacrylic acid polymer

20

The pH of a composition according to the invention is normally adjusted so as to establish a balance so that i) the solubility of the active substance in the composition is at the most 0.2 mg/ml and ii) the mucoadhesive properties of the polyacrylic acid polymer is maintained sufficiently high to obtain a therapeutically and/or prophylactically effective concentration of the active substance in the lacrymal fluid of the eye for at least about 6 hours as assessable in the rabbit eye test as described herein.

25

30

With respect to the swelling of the polyacrylic acid polymer in a composition according to the invention, the swelling should be of such a order of magnitude that the resulting composition has a viscosity in a range of from about 20 mPas

to about 3000 mPas such as, e.g., from about 100 mPas to about 3000 mPas, from about 500 mPas to about 3000 mPas, from about 1000 to about 2800 mPas or from about 1500 mPas to about 2500 mPas such as, e.g., 1500 mPas as measured on a Haake VT500 Viscosimeter at a temperature of 20 °C and at
5 a shear rate of 100 s⁻¹.

Preferably, the viscosity of the composition is at least 1500 mPas so that upon application to the eye the composition is maintained *in situ* and releases the active substance from the composition in a prolonged manner during at least 6-
10 8 hours as assessable in the rabbit eye test as described herein.

Furthermore, an important feature of a composition of the invention is its ability to precipitate the polyacrylic acid polymer in the *fornix inferior* under the eye lid once the composition has been applied to the eye. By precipitation of the
15 composition it is ensured that the composition is maintained *in situ* and the risk of elimination of the composition by tear turnover or an increase in lacrimation is significantly reduced. Accordingly, a prolonged release is obtainable which would not be the case if the composition is quickly eliminated from the eye. Moreover, the localisation of the composition under the eye lid is very
20 favourable as the composition is not spread over the whole eye mucosa which could lead to an unwanted blurred vision or precipitation of the composition or parts of the composition on the eye surface.

The precipitation of the composition after application to the eye is due to a
25 salting out of the polymeric substance(s) included in the composition. In order to test whether a composition fulfils the above-mentioned requirement with respect to precipitation *in situ* the following test can be employed:

1 ml of an aqueous solution of 0.9% sodium chloride is added to 1 g of the
30 composition at room temperature. An out-salting effect is evidenced visually by the naked eye as a precipitation of the polyacrylic acid polymer.

Suitable compositions according to the invention may be administered in the form of eye drops or – like an ointment - in the form of a hydrogel. The composition may be in unit dosage form for administration of a single dose or it may be in a dosage form containing more than one dose.

5

A composition according to the invention may further comprise a pharmaceutically acceptable excipient.

10

Suitable pharmaceutically acceptable excipients for use in a composition according to the invention include:

solvents like, e.g., water,

15

pH adjusting agents like, e.g. sodium hydroxide and hydrochloric acid,

isotonic adjusting agents like, e.g., glycerol, mannitol, sorbitol, xylitol and the like,

20

gelling agents like, e.g., cellulose derivatives which do not precipitate at a temperature of above about 30 °C such as, e.g., hydroxyethylcellulose, hydroxypropylmethylcellulose and the like, and polymers from the Pluronic® series,

25

viscosity-adjusting agents like, e.g., hydroxyethylcellulose and hydroxypropylmethylcellulose,

preservatives like, e.g., benzalkonium chloride, parabenes, chlorohexidine, chlorohexidine gluconate and chlorohexidine acetate,

30

chelating agents like, e.g., EDTA,

stabilisers like, e.g., antioxidants such as, e.g., tocopherol, tocopherol acetate, butylhydroxytoluene and butylhydroxyanisol.

5 A composition according to the invention may further include a further therapeutically and/or prophylactically active substance, e.g. for use in relevant combination therapy. An especially interesting group of active substances in this context is the steroids, e.g. dexamethasone.

10 A composition according to the invention is typically in the form of eye drops, viscous eye drops or in the form of an ointment. The amount applied of the composition depends on the specific formulation and the device from which it is to be administered. In general, the amount of the composition applied contains a sufficient amount of the active substance (i.e. in general from about 10 μg to about 300 μg such as, e.g. from about 10 μg to about 200 μg , from about 10 μg to about 100 μg , from about 12 μg to about 50 μg , from about 15 μg to about 30 μg or from about 20 μg to about 25 μg). When the composition is
15 administered in the form of eye drops e.g. from a tube, the amount applied is normally about 15-40 μl such as, e.g. in a range corresponding to 20-30 μl .

20 A composition according to the invention is normally intended for use once or twice daily, but in certain situations administration more frequent (e.g. trice daily) can be desired.

A composition according to the invention is one obtainable by dispersing the active substance in a gel-forming aqueous vehicle. The active substance is normally dispersed in the gel-forming aqueous vehicle in the form of a
25 suspension comprising the active substance in an aqueous medium and, optionally, a pharmaceutically acceptable excipient.

30 The gel-forming vehicle can be obtained by i) dispersing a polyacrylic acid polymer in water which, optionally, comprises a pharmaceutically acceptable excipient, followed by ii) adjusting pH of the thus obtained gel-forming aqueous vehicle to a pH in a range of from about 6.5 to about 8.5, such as, e.g., from about 7 to about 8, from about 7.2 to about 7.6, such as e.g. about 7.4.

In another aspect, the invention relates to a method for the preparation of a composition according to the invention, the method comprises dispersing the active substance in an aqueous gel-forming vehicle.

5 More specifically, a method according to the invention comprises the steps of:

- i) suspending the active substance in an aqueous medium optionally comprising a pharmaceutically acceptable excipient,
- ii) sterilising the thus obtained suspension to obtain a sterile suspension,
- 10 iii) milling the thus obtained sterile suspension to obtain a suspension wherein the particle size meets the requirements with respect to particle size as described under "Eye-drops" in Ph. Eur. 3rd Ed. 1997, page 1762,
- iv) dispersing a polyacrylic acid polymer in an aqueous medium optionally comprising a pharmaceutically acceptable excipient to obtain a dispersion,
- 15 v) adjusting the pH of the dispersion of the polyacrylic acid polymer to a pH in a range of from about 6 to about 8.5, such as, e.g., from about 7 to about 8, from about 7.2 to about 7.6, such as e.g. about 7.4,
- vi) adding the suspension obtained from step iii) to the aqueous gel-forming vehicle obtained from step v).

20

Normally, the dispersion containing the polyacrylic acid polymer has to be sterilised, and, therefore, the method may comprise a further step of sterilising the dispersion of the polyacrylic acid polymer in a step before step vi). This step may either be before step v) or after step v) above. The sterilisation is

25 performed by methods well known by a person skilled in the art such as by autoclaving the dispersion at 121 °C for 15 min or any other proper temperature-time relationship.

In a still further aspect, the invention relates to a method for the treatment

30 and/or prophylaxis of eye diseases like eye infections of a mammal comprising administering to a mammal in need thereof a prolonged release ophthalmic composition according to the invention.

A method for the treatment and/or prophylaxis of eye diseases like eye infections comprises administering the prolonged release composition once or twice daily.

- 5 In a further aspect, the invention relates to a method for administering a therapeutically and/or prophylactically active substance selected from the group consisting of a fluoroquinolone, a fluoroquinolone derivative and a pharmaceutically acceptable salt thereof to an eye of a mammal, the method comprising applying the active substance in the form of a prolonged
10 composition to the *fornix inferior* of the eye.

Specific compositions according to the invention comprise typically

| | | |
|----|---|------------------|
| 15 | Fluoroquinolone (e.g. NM394) | 3.0 mg \pm 10% |
| | Polyacrylic acid polymer (e.g. Carbopol® 974P) | 5.0 mg \pm 50% |
| | Water, sterile | up to 1 ml |

- 20 The compositions are normally adjusted to a pH of 7.2-7.6 with a solution of sodium hydroxide. Pharmaceutically acceptable excipients may also be present such as, e.g. pr. ml of the composition:

| | | |
|----|---|-------------------|
| 25 | Preservative (e.g. benzalkonium chloride) | 0.05 mg \pm 20% |
| | Isotonic adjusting agent (e.g. glycerol 85%) | 22.0 mg \pm 10% |

EXPERIMENTAL SECTION

- 30 **Determination of the solubility of a fluoroquinolone**

The solubility of a specific fluoroquinolone in isotonic phosphate buffer solution

is determined at a pH in a range of 6.5 to 8.0 and at temperatures at 24°C and 34°C, where the latter represents the tear liquid temperature, being in an interval of 30-35°C. A surplus of the fluoroquinolone in question is shaken for three days with each buffer solution. The suspension are centrifuged and the supernatant is diluted with buffer. The content of fluoroquinolone is determined by UV measurements at the maximum (about 272 nm for NM394) and calculation against a standard. All experiments in duplicate.

The isotonic phosphate buffer solution was prepared as follows. Isotonic solutions of disodium hydrogen phosphate (0.13 M) and sodium dihydrogen phosphate (0.18 M) were prepared. Solution with pH 6.5, 7.0 and 8.0 were prepared by mixing different ratios of the two isotonic solutions.

The following results were obtained:

| pH | Solubility at 24°C µg/ml | Solubility at 32- 34°C µg/ml |
|-----|-----------------------------|------------------------------------|
| 6.5 | 181 | 193 |
| 7.0 | 137 | 167 |
| 7.4 | 131 | 160 |
| 8.0 | 142 | 186 |

Determination of NM394

Quantitative assay of NM394: The ophthalmic composition is dissolved in acetonitrile: methanol: 1% acetic acid 60:10:30. The carbomer polymer is precipitated by adding a small amount of KNO₃ and is removed by centrifugation. The solution is diluted appropriately with mobile phase: acetonitrile: methanol:0.015 M phosphoric acid:sodium laurylsulfate 0.1M 270:310:395:25. The assay is performed by reversed phase HPLC at 50 °C

(column oven) using UV detection at 254 nm. 4-ethoxybenzoic acid is used as an internal reference.

Determination of particle size

5

A suitable quantity of the composition is introduced with a micropipette onto a slide and an area corresponding to 10 µg of the solid phase is scanned under a microscope. For practical reasons, the whole sample is first scanned at low magnification (e.g. x 50) and particles greater than 25 µm are identified. These larger particles can then be measured at a large magnification (e.g. x 200 to x 500). Not more than 20 particles have a maximum dimension greater than 50 µm, and not more than two of these particles have a maximum dimension greater than 50 µm. None of the particles has a maximum dimension greater than 90 µm.

15

Rabbit eye test

The rabbit eye test referred to in the description and in the claims is performed in accordance with the details given in the following example 1.

20

Example 1

Pre-clinical kinetic studies of NM394 viscous eye drops – Biopharmacokinetics in lacrymal fluid

25

In vivo biopharmacokinetics

An eye composition having the following composition per ml was prepared:

30

Composition I:

NM 394

3.00 mg

| | | |
|---|------------------------------------|----------|
| | Carbopol® 974P | 5.00 mg |
| | Glycerol 85% Ph. Eur. | 22.00 mg |
| | Benzalkonium chloride | 0.05 mg |
| | Sodium hydroxide 5N for pH 7,0-8,0 | q.s. |
| 5 | Water for inj., to make | 1 ml |

NM394 was obtained from Nippon, Shinyaku Co. Ltd., Japan which has developed the compound in corporation with Meiji Seika, Co. Ltd., Japan. NM394 can be prepared according to the method disclosed in US-A-4,843,070 (Nippon, Shinyaku Co., Ltd., Japan). All other ingredients employed were of pharmacopoeia standard.

In a small vessel NM394 was suspended in a 0.01% w/v benzalkonium chloride solution. Milling beads were added to the suspension. The mixture were sterilised by autoclaving at 121°C for 15 min and then milled according to Ph..Eur.'s standard for particles in ophthalmic formulations (cf. above). The resulting particle size was preferably in a range of 2-5 µm for the majority of the particles.

In the processing vessel glycerol 85% was dissolved in sterile water. The Carbopol® 974P was dispersed aseptically in the solution and sterilised by autoclaving at 121°C for 15 min. The dispersion was cooled and the rest of the benzalkonium chloride was added aseptically as a sterile solution. The mixture was neutralised by addition of sterile sodium hydroxide solution. Finally the milling beads were separated aseptically from the autoclaved and milled NM394 suspension and the suspension was added aseptically to the gel vehicle.

The composition (in the following called Composition I) thus prepared was compared with a composition analogue to Composition I but with 0.1 mg benzalkonium chloride (denoted "BAK" in the following tables) instead and employing another crystal modification of NM394 (Composition II) and with two conventional eyedrop compositions, one with 0,3% w/v Norfloxacin (Zoroxin®MDS) and one with 0,3% w/v Ofloxacin (Exocin®).

The crystal modifications of NM394 employed have been characterised by the X-ray diffraction pattern. The results are given in Figure 1.

5 The four compositions were compared in the following manner:

Ten Himalayan rabbits weighing about 2.5 kg were used in the studies. They were designated Nos. 1-10, numbered by ear tags, and placed in restraining boxes during the first 6 hours of the investigation period and at 24 hours
10 sampling. Between treatment 8, 12 and 24 hours sampling the animals were housed individually and given pelleted food (Altromin® 2123) and water *ad libitum*.

Samples for microbiologic determination were taken by placing 6.0 mm AA
15 discs (Watmann®) in the *fornix inferior*, closing the eye lids for approximately 10 seconds and removing the discs with forceps. The discs were placed on the surface of agar dishes, 14 cm in diameter, inoculated with *Micrococcus leuteus* ATCC9341 when determining high concentrations of NM394 and *Escherichia coli* HA2 when determining lower concentrations and discs with samples of
20 Norfloxacin or Ofloxacin together with discs on which 30µl of NM394, Norfloxacin or Ofloxacin standard solutions, respectively, have been placed. The standard solutions of NM394 were prepared in phosphate buffer pH 8.0. The 30µl volume is equivalent to that amount which the discs absorb.

25 The petri dishes were incubated for 16-18 hours at the optimum temperature for the test organisms in question (28 °C for *M. luteus* and 22 °C for *E. coli*). The inhibition zones of the samples were measured to the nearest 0.1 mm with needle point calliper and interpolated on the standard curve which was established as the best response line from the inhibition zone for the standard
30 solutions.

Prior to each investigation the lacrymal fluid of each rabbit was tested for the absence of inhibitory substance to the most sensitive of the test organisms. One

drop of each of the four formulations, respectively, was instilled in the *fornix inferior* of the right or left eye of the rabbits. Samples were taken at ½, 1, 2, 4, 6 and 24 hours following treatment (A) and only at 24 hours following treatment (B) with Norfloxacin and Ofloxacin, but at 8, 16 and 24 hours after treatment (B) for the two formulations of NM394.

The results presented in table1 show that the two compositions of NM394 have measurable concentrations in all rabbits 6 hours after treatment and that Composition II also have measurable concentrations in all rabbits after 24 hours (Experiment A). From the same table no difference is noted between the two compositions of NM394 with different crystal modifications, even when the number of samples were increased with 8 and 16 hours (experiment B).

Following treatment A with Norfloxacin and Ofloxacin (table 2) the mean values are very similar but also much lower than for NM394. It is also noted that only four rabbits with Norfloxacin and one with Ofloxacin have been measurable concentrations at 24 hours.

In figure 2 is shown the results from the above-mentioned experiments. The figure shows mean the concentration of the fluoroquinolone in the lacrymal fluid *versus* the time after administration. The minimum inhibiting concentration (MIC) is about 1 µg/ml (i.e. the minimal effective concentration). From fig. 2 it is seen that the MIC value is reached after about 5-6 hours after administration of Zoroxin and Exocin eye drops, respectively, i.e. the effect of these compositions is at the most about 5-6 hours. To the contrary, the compositions according to the invention exhibited a concentration in the lacrymal fluid exceeding that of MIC for about 24 hours, i.e. indicating that the compositions according to the invention are suitable for administration once (or twice) daily.

Thus it may be concluded that the composition of NM394 in 0.5% w/v Carbopol® 974P was found to possess a favourable biopharmacokinetic profile

superior to that of the two commercial available fluoroquinolone preparations.

Table 1

A: Sample removal at 0, ½, 1, 2, 4, 6 and 24 hours
 B: Sample removal at 0, 8, 16 and 24 hours

| Composition | Animal | mcg Norfloxacin per ml lacrimal fluid | | | | | | | | | | | | | | | | Mean | |
|--|--------|---------------------------------------|---------|---|-----|-----|-----|------|------|------|------|------|------|------|------|------|--|-----------------|-----------------|
| | | Hours after treatment | | | | | | | | | | | | | | | | A ¹⁾ | B ²⁾ |
| | | | | | | | | | | | | | | | | | | | |
| | | No. | Ear-tag | 0 | ½ | 1 | 2 | 4 | 6 | 24 | 0 | 8 | 16 | 24 | | | | | |
| Composition I 97 231 43A-01 0.3% NM394 (MME 10) in 0.5% Carbopol 974P (+ BAK 0.05) | | 1 | 378/R | - | 244 | 378 | 19 | 7.8 | 2.1 | - | - | 1.8 | 0.16 | - | 0.26 | 0.86 | | | |
| | | 2 | 405/R | - | 184 | 110 | 27 | 8.7 | 2.7 | 0.08 | - | 0.40 | 0.12 | 3.3 | | | | | |
| | | 3 | 399/R | - | 373 | 39 | 43 | 13 | 1.7 | 0.08 | - | 1.3 | 2.7 | 0.06 | | | | | |
| | | 4 | 396/R | - | 438 | 237 | 212 | 15 | 7.3 | 0.10 | - | 1.3 | 0.59 | 0.08 | | | | | |
| | | 5 | 374/R | - | 373 | 143 | 123 | 68 | 1.7 | - | 0.32 | - | 0.34 | | | | | | |
| | | 6 | 403/R | - | 318 | 171 | 29 | 28 | 27 | - | 2.1 | 0.44 | 0.78 | | | | | | |
| | | 6 | 409/R | - | 179 | 353 | 143 | 17 | 11 | 0.44 | - | 0.53 | 0.69 | 1.4 | | | | | |
| | | 8 | 415/R | - | 484 | 282 | 19 | 14 | 3.4 | 0.62 | - | 3.6 | - | 0.95 | | | | | |
| | | 9 | 414/R | - | 378 | 63 | 29 | 4.5 | 0.23 | - | 0.18 | - | 15* | | | | | | |
| | | 10 | 412/R | - | 323 | 244 | 49 | 13 | 37 | 1.3 | - | 3.1 | - | 12* | | | | | |
| Mean | | | | | 329 | 202 | 69 | 19 | 9.4 | 0.26 | - | 1.5 | 0.47 | 0.86 | | | | | |
| Composition II 97 232 43A-01 0.3% NM394 (MME 72-2) in 0.5% Carbopol 974P (+ BAK 0.10) | | 1 | 378/L | - | 343 | 89 | 121 | 11 | 14 | 0.11 | - | 1.9 | - | 0.46 | 0.59 | 0.72 | | | |
| | | 2 | 405/L | - | 264 | 155 | 25 | 6.2 | 8.2 | 1.2 | - | 1.3 | - | - | | | | | |
| | | 3 | 399/L | - | 270 | 245 | 52 | 29 | 3.4 | 0.39 | - | 0.71 | 0.51 | 0.28 | | | | | |
| | | 4 | 396/L | - | 232 | 192 | 129 | 8.8 | 6.0 | 0.81 | - | 0.15 | - | 2.6 | | | | | |
| | | 5 | 374/L | - | 163 | 146 | 46 | 30 | 8.4 | 0.03 | - | 0.23 | - | 0.27 | | | | | |
| | | 6 | 403/L | - | 328 | 214 | 148 | 25 | 33 | 0.57 | - | 1.1 | 0.13 | - | | | | | |
| | | 7 | 409/L | - | 161 | 123 | 73 | 41 | 10 | 1.2 | - | 7.9 | 0.24 | 0.82 | | | | | |
| | | 8 | 415/L | - | 227 | 212 | 123 | 13 | 3.5 | 0.78 | - | 1.4 | 0.45 | 0.07 | | | | | |
| | | 9 | 414/L | - | 125 | 104 | 24 | 7.2 | 5.9 | 0.69 | - | 1.1 | 4.0 | 2.6 | | | | | |
| | | 10 | 412/L | - | 179 | 92 | 77 | 0.71 | 0.39 | 0.14 | - | 1.3 | - | 0.07 | | | | | |
| Mean | | | | | 229 | 157 | 82 | 17 | 9.3 | 0.59 | - | 1.7 | 0.53 | 0.72 | | | | | |

(-): <0.06 mcg/g R: right eye L: left eye *: omitted

Table 2

Concentrations of Norfloxacin and Ofloxacin in lacrimal fluid after administration of 1 drop (approx. 30 μ l) Norfloxacin 0.3% eye drop and Ofloxacin 0.3% eye drop, respectively, into rabbit eye

| Batch No | Animal | | mcg Norfloxacin per ml lacrimal fluid Hours after treatment | | | | | | | | | | Mean | |
|-------------------------|--------|-------|--|----------|-----|------|------|------|------|-----------------|------|-----------------|-----------------|--|
| Composition | | Ear- | A ¹⁾ | | | | | | | B ²⁾ | | A ¹⁾ | B ²⁾ | |
| | | tag | 0 | ½ | 1 | 2 | 4 | 6 | 24 | 0 | 24 | 24 | 24 | |
| 95J01 | 1 | 378/R | - | 27 | 11 | 3.2 | 1.2 | 0.13 | - | - | 2.2 | | | |
| | 2 | 405/R | - | 4.8 | 3.0 | - | - | - | - | - | 2.1 | | | |
| | 3 | 399/R | - | 72 | 72 | 22 | 2.8 | 1.5 | - | - | 0.28 | | | |
| ZOROXIN® MSD | 4 | 396/R | - | 17 | 1.0 | 3.4 | 0.34 | 0.13 | 0.40 | - | - | | | |
| 0.3% Norfloxacin | 5 | 374/R | - | 38 | 19 | 22 | 7.0 | 3.9 | - | - | - | | | |
| | 6 | 403/R | - | >45 * | 14 | 22 | 1.8 | 1.1 | 0.17 | - | - | 0.24 | 0.54 | |
| | 7 | 409/R | - | 13 | 2.1 | 1.7 | 0.87 | 0.26 | - | - | - | | | |
| (+ BAK 0.025 mg/ml) | 8 | 415/R | - | 38 | 9.7 | 0.63 | 7.9 | 1.2 | 0.28 | - | NS | | | |
| | 9 | 414/R | - | 12 | 2.5 | 1.4 | 0.81 | 0.17 | - | - | 0.29 | | | |
| | 10 | 412/R | - | 7.6 | 27 | 4.4 | 2.7 | 0.41 | 1.5 | - | - | | | |
| Mean | | | | 25 | 18 | 8.1 | 2.5 | 0.88 | 0.24 | | 0.54 | | | |

| Batch No | Animal | | mcg Ofloxacin per ml lacrimal fluid Hours after treatment | | | | | | | | | | Mean | |
|------------------------|--------|-------|--|----------|------|------|------|------|------|-----------------|------|-----------------|-----------------|--|
| Composition | | Ear- | A ¹⁾ | | | | | | | B ²⁾ | | A ¹⁾ | B ²⁾ | |
| | | tag | 0 | ½ | 1 | 2 | 4 | 6 | 24 | 0 | 24 | 24 | 24 | |
| EB0701 | 1 | 378/R | - | 12 | 0.33 | 38 | 0.68 | 0.64 | - | - | 1.5 | | | |
| | 2 | 405/R | - | 11 | 5.0 | 1.6 | 1.3 | 1.2 | 0.86 | - | 0.3 | | | |
| | 3 | 399/R | - | 53 | 27 | 25 | 14 | 4.7 | - | - | 0.51 | | | |
| EXOCIN® | 4 | 396/R | - | 61 | 4.9 | 2.9 | 1.9 | 3.5 | - | - | - | | | |
| (ALLERGAN) | 5 | 374/R | - | 26 | 58 | 10 | 0.54 | 0.42 | - | - | 1.7 | | | |
| 0.3% Ofloxacin | 6 | 403/R | - | 3.2 | 4.0 | 3.0 | 0.22 | 0.47 | - | - | - | 0.09 | 0.67 | |
| | 7 | 409/R | - | 4.9 | 0.95 | 0.80 | 0.22 | - | - | - | - | | | |
| | 8 | 415/R | - | 60 | 28 | 4.6 | 0.34 | 0.50 | - | - | 1.4 | | | |
| (+ BAK 0.05 mg/ml) | 9 | 414/R | - | 1.8 | 9.2 | 0.22 | 0.36 | - | - | - | 0.58 | | | |
| | 10 | 412/R | - | >70 * | 46 | 0.54 | - | - | - | - | 12* | | | |
| Mean | | | | 26 | 18 | 8.7 | 2.0 | 1.1 | 0.09 | | 0.67 | | | |

1) A: SAMPLE REMOVAL AT 0, ½, 1, 2, 4, 6 AND 24 HOURS

2) B: SAMPLE REMOVAL AT 0 AND 24 HOURS

(-): < 0.19 mcg/ml *: Omitted R: Right eye NS: No sample

Example 2**Serum concentrations of NM394 following topical administration to the eye**

5

Topical application of NM394 viscous eye drop in the eye would not give rise to systemic activity because no antibiotic concentration was detected in the serum at ½, 2, 5 and 24 hours following application of one drop 1% w/v NM394 in 0.5% w/v Carbopol® 974P to five rabbits (NZW). The concentrations of NM394 in the lacrymal fluid were at the same level as reported in Example 1.

10

Overall conclusions

Following application of one drop 0.3% w/v NM394 viscous eye drop in 0.5% w/v Carbopol® 974P all rabbits have measurable concentrations in the lacrymal fluid 6 hours after the treatment and six out of ten rabbits have also measurable concentrations at 24 hours.

15

After the same treatment schedule only 40% of the rabbits with Zoroxin® and 10% with Exocin® have measurable concentrations at 24 hours.

20

However, treatment with the compositions according to the invention resulted generally in higher concentrations of the active substance in the lacrymal fluid after 24 hours whether samples were taken according to experiment A or B. In general the results obtained at 24 hours were about 2 to 10 times higher when compositions according to the invention were applied compared with the marketed compositions.

25

No systemic activity would be expected because no antibiotic concentration was detected in the serum following application in the eye of one drop of a formulation with 1% w/v NM394 in 0.5% w/v Carbopol® 974P to five NZW rabbits.

30

CLAIMS

1. A pharmaceutical prolonged release ophthalmic composition for human and veterinary use comprising as a therapeutically and/or prophylactically active substance a fluoroquinolone, a fluoroquinolone derivative or a pharmaceutically acceptable salt thereof dispersed in a gel-forming aqueous vehicle.
2. A composition according to claim 1, wherein the active substance is released from the composition in such a manner so as to obtain a therapeutically and/or prophylactically effective concentration in the lacrymal fluid of the eye for at least about 6 hours such as, e.g., about 6.5 hours, 7 hours, 7.5 hours or 8 hours as assessable in the rabbit eye test as described herein.
3. A composition according to claim 1 or 2 for administration to the eye once or twice daily.
4. A composition according to any of the preceding claims for use in the treatment and/or prophylaxis of eye diseases such as, e.g. eye infections.
5. A composition according to any of the preceding claims, wherein the fluoroquinolone is selected from the group consisting of: ofloxacin, ciprofloxacin, norfloxacin, lomefloxacin, enoxacin, premafloxacin, fleroxacin, prulifloxacin and 6-fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4H-[1,3]-thiazeto[3,2-a]-quinoline-3-carboxylic acid (NM 394).
6. A composition according to any of the preceding claims, wherein the solubility of the active substance is at the most about 0.3 mg/ml such as e.g. about 0.25 mg/ml, about 0.2 mg/ml, about 0.15 mg/ml, about 0.125 mg/ml or about 0.1 mg/ml as determined in isotonic phosphate buffer at a pH of 7.0-7.4 and at a temperature of 32-34 °C.

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7. A composition according to any of the preceding claims, wherein the solubility of the active substance in the composition is at the most about 0.3 mg/ml such as e.g. about 0.25 mg/ml, about 0.2 mg/ml, about 0.15 mg/ml, about 0.125 mg/ml or about 0.1 mg/ml at room temperature.
8. A composition according to any of the preceding claims, wherein the active substance is NM 394.
- 10
9. A composition according to any of the preceding claims, wherein the concentration of the active substance in the composition is sufficiently high to obtain a therapeutically effective concentration in the eye after administration.
- 15
10. A composition according to any of the preceding claims, wherein the gel-forming aqueous vehicle comprises an ophthalmically acceptable cross-linked polyacrylic acid polymer
- 20
11. A composition according to claim 10, wherein the cross-linked polyacrylic acid polymer has mucoadhesive properties.
- 25
12. A composition according to claim 10 or 11, wherein the polyacrylic acid polymer is cross-linked with polyalkenyl ethers or divinyl glycol.
13. A composition according to claim 10 or 11, wherein the polyacrylic acid polymer is a carbomer belonging to one of the following series: Acrisint®, Acritamer®, Carbopol®, PerForMex®, Syntalen®, Thixol® and Noveon®.
- 30
14. A composition according to claim 10 or 11, wherein the polyacrylic acid polymer is a carbomer selected from the group consisting of Carbopol® resins and Noveon® polycarbophils.
15. A composition according to claim 14, wherein the polyacrylic acid polymer is a Carbopol® resin.

16. A composition according to claim 15, wherein the polyacrylic acid polymer is Carbopol® 974P.
- 5 17. A composition according to any of claims 10-16, wherein the concentration of the polyacrylic acid polymer in the composition is in a range of from about 0.1 to about 5% w/v such as, e.g. from about 0.1 to about 4% w/v, from about 0.2 to about 3% w/v, from about 0.2 to about 2% w/v, from about 0.2 to about 1.5% w/v or from about 0.3 to about 1.0% such as, e.g., about 0.5% w/v.
- 10 18. A composition according to any of the preceding claims, wherein the pH is in a range of from about 6 to about 8.5, such as, e.g., from about 7 to about 8, from about 7.2 to about 7.6, such as e.g. about 7.4.
- 15 19. A composition according to any of claims 11-18, wherein the pH of the composition is adjusted so as to balance that i) the solubility of the active substance in the composition is at the most about 0.2 mg/ml and ii) the mucoadhesive properties of the polyacrylic acid polymer is maintained sufficiently high to obtain a therapeutically and/or prophylactically effective concentration of the active substance in the lacrymal fluid of the eye for at least about 6 hours as assessable in the rabbit eye test as described herein.
- 20 20. A composition according to any of the preceding claims having a viscosity in a range of from about 20 mPas to about 3000 mPas such as, e.g., from about 100 mPas to about 3000 mPas, from about 500 mPas to about 3000 mPas, from about 1000 to about 2800 mPas or from about 1500 mPas to about 2500 mPas as measured on a Haake
- 25 30 Viscosimeter VT500 at a temperature of 20 °C and at a shear rate of 100 s⁻¹.

- 5
21. A composition according to claim 20, wherein the viscosity of the composition is at least 1500 mPas and the active substance is released from the composition in a prolonged manner during at least 6-8 hours as assessable in the rabbit eye test as described herein.
22. A composition according to any of the claims 10-21, wherein the active substance is NM 394 and the polyacrylic acid polymer is Carbopol® 974P.
- 10 23. A composition according to any of the preceding claims further comprising a pharmaceutically acceptable excipient.
- 15 24. A composition according to claims 10-23, which – when 1 ml of an aqueous solution of 0.9% sodium chloride is added to 1 g of the composition – results in an out-salting of the polyacrylic acid polymer as evidenced visually by the naked eye as a precipitation of the polyacrylic acid polymer.
- 20 25. A composition according to any of the preceding claims, the composition being one obtainable by dispersing the active substance in a gel-forming aqueous vehicle.
- 25 26. A composition according to claim 25, wherein the active substance is dispersed in the gel-forming aqueous vehicle in the form of a suspension comprising the active substance in an aqueous medium and, optionally, a pharmaceutically acceptable excipient.
- 30 27. A composition according to claims 25 or 26, wherein the gel-forming aqueous vehicle is obtained by i) dispersing a polyacrylic acid polymer in water which, optionally, comprises a pharmaceutically acceptable excipient, followed by ii) adjusting pH of the thus obtained gel-forming aqueous vehicle to a pH in a range of from about 6 to about 8.5, such as, e.g., from about 7 to about 8, from about 7.2 to about 7.6, such as e.g. about 7.4.

28. A method for the preparation a composition according to any of claims 1-27 comprising dispersing the active substance in an aqueous gel-forming vehicle.

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29. A method according to claim 28 comprising the steps of:

- i) suspending the active substance in an aqueous medium optionally comprising a pharmaceutically acceptable excipient,
- 10 ii) sterilising the thus obtained suspension to obtain a sterile suspension,
- iii) milling the thus obtained sterile suspension to obtain a suspension wherein the particle size meets the requirements with respect to particle size as described under "Eye-drops" in Ph. Eur. 3rd Ed. 1997, page 1762,
- 15 iv) dispersing a polyacrylic acid polymer in an aqueous medium optionally comprising a pharmaceutically acceptable excipient to obtain a dispersion,
- v) adjusting the pH of the dispersion of the polyacrylic acid polymer to a pH in a range of from about 6 to about 8.5, such as, 20 e.g., from about 7 to about 8, from about 7.2 to about 7.6, such as e.g. about 7.4,
- vi) adding the suspension obtained from step iii) to the aqueous gel-forming vehicle obtained from step v).

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30. A method according to claim 29 further comprising a step of sterilising the dispersion of the polyacrylic acid polymer in a step before step vi).

31. A method for the treatment and/or prophylaxis of eye diseases like eye infections of a mammal comprising administering to a mammal in need thereof a prolonged release ophthalmic composition according to any of claims 1-27.

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32. A method according to claim 31 comprising administering the prolonged release composition once or twice daily.

33. A method for administering a therapeutically and/or prophylactically active substance selected from the group consisting of a fluoroquinolone, a fluoroquinolone derivative and a pharmaceutically acceptable salt thereof to an eye of a mammal, the method comprising applying the active substance in the form of a prolonged composition to the *fornix inferior* of the eye.

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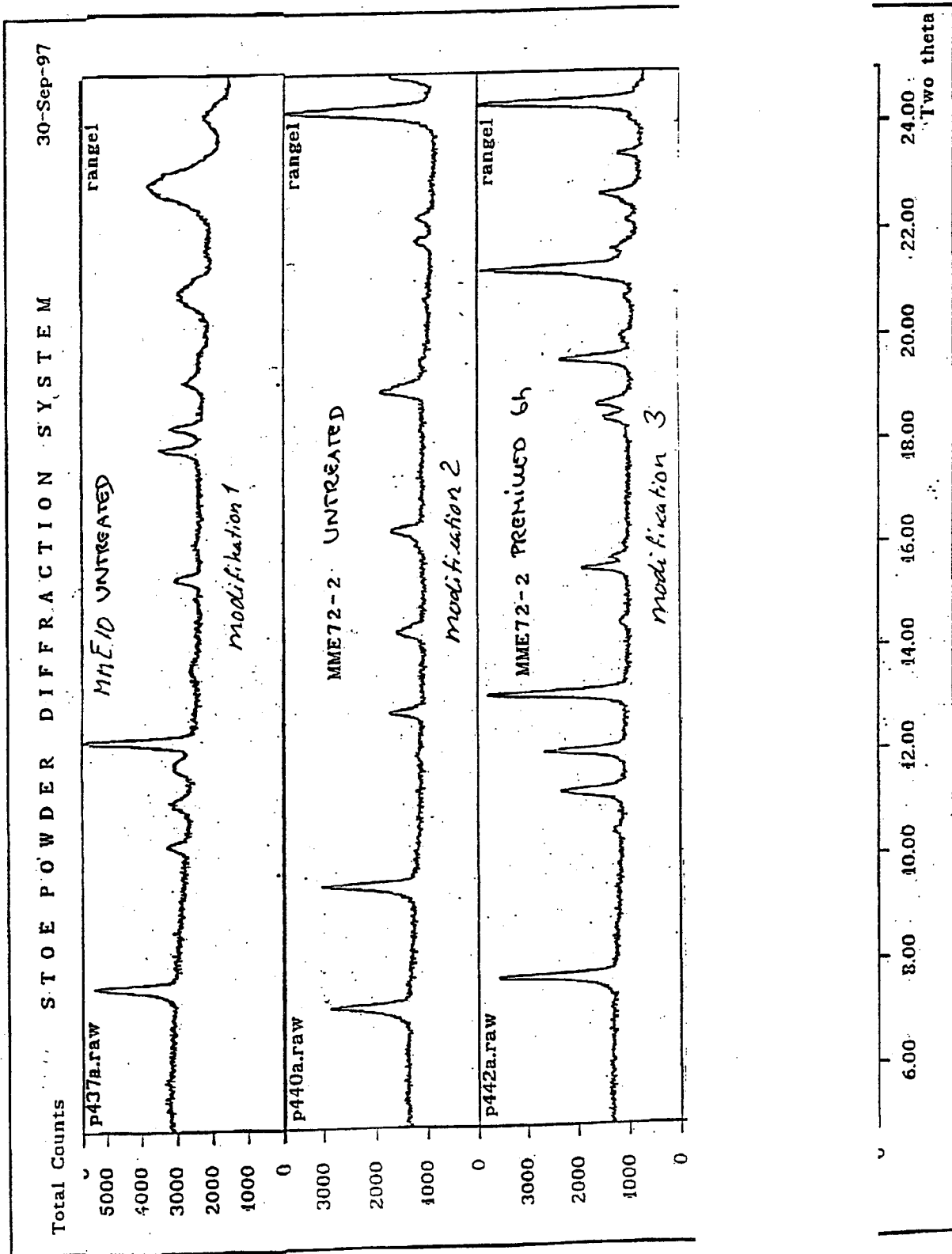


Fig. 1

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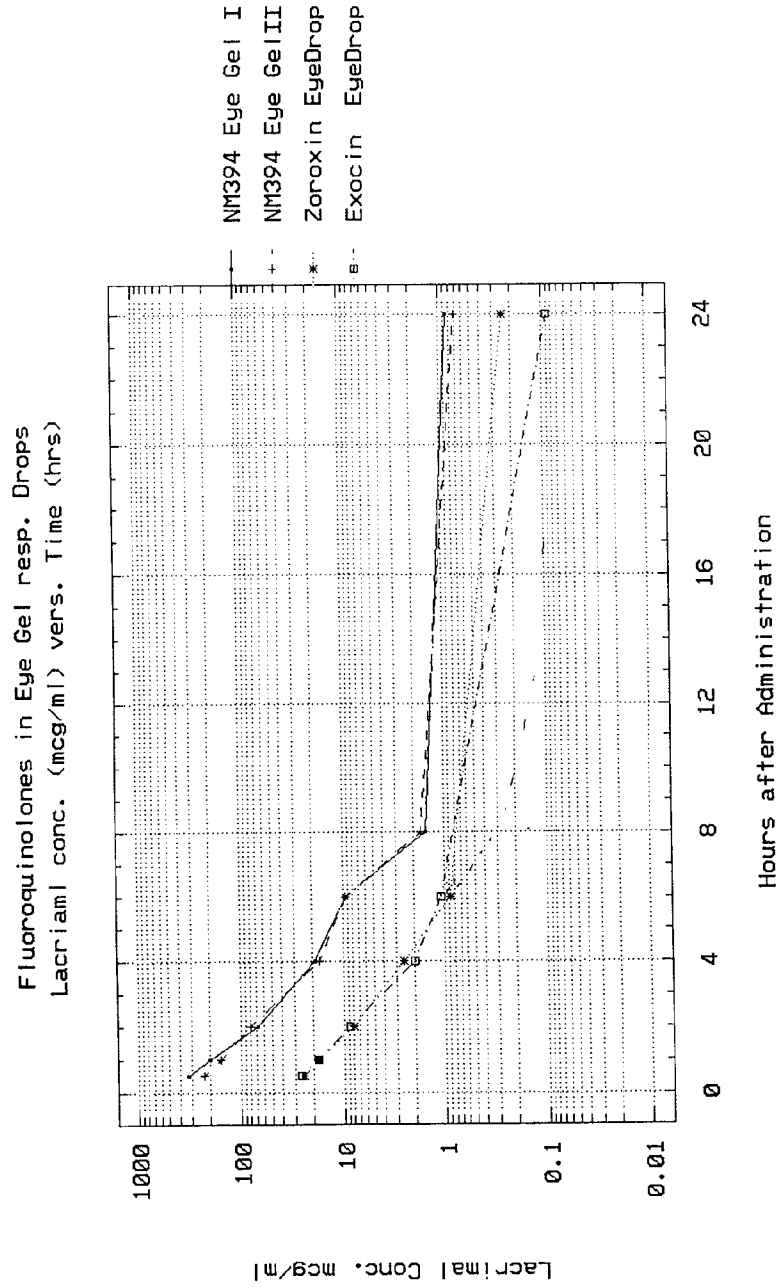


Fig. 2

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 99/00348

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/06 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|--|
| X | <p>FR 2 678 832 A (EUROPHTA SA LABORATOIRE) 15 January 1993 (1993-01-15)</p> <p>page 1, line 7-9 page 2, line 1-9 page 2, line 34 -page 3, line 4 page 3, line 15-17 page 4, line 6-9 page 4, line 27-30 page 5, line 17-24 page 6, line 1,2 example 2 claims 1-3,5,6,9</p> <p>---</p> <p>-/--</p> | <p>1-5, 9-15,17, 18,23, 26-28, 31-33</p> |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 October 1999

Date of mailing of the international search report

15/10/1999

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Authorized officer

La Gaetana, R

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 99/00348

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|-----------------------------------|
| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | US 5 631 004 A (CAGLE GERALD D ET AL) 20 May 1997 (1997-05-20) column 2, line 19-22 column 2, line 56-65 column 4, line 22-29 column 4, line 63-66 column 5, line 4-9 example 1 table 2 column 10, line 3-5 claims --- | 1-5, 9-15, 17, 28, 31-33 |
| X | EP 0 590 786 A (ALCON LAB INC) 6 April 1994 (1994-04-06) page 2, line 34, 35 page 3, line 31-37 examples 6, 8 --- | 1, 3-5, 9-18, 25, 28, 31-33 |
| A | WO 98 25620 A (ALCON LAB INC) 18 June 1998 (1998-06-18) examples 3, 5 claims 1, 3, 7, 13 ----- | 29, 30 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 99/ 00348

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 31-33 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 99/00348

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|--|--|
| FR 2678832 A | 15-01-1993 | AT 165732 T AU 2360592 A DE 69225405 D DE 69225405 T EP 0594760 A ES 2118824 T FI 940081 A WO 9300887 A NO 940064 A | 15-05-1998 11-02-1993 10-06-1998 03-12-1998 04-05-1994 01-10-1998 07-03-1994 21-01-1993 04-03-1994 |
| US 5631004 A | 20-05-1997 | NONE | |
| EP 0590786 A | 06-04-1994 | AT 160503 T AU 666957 B AU 4440193 A CA 2104917 A,C DE 69315406 D DE 69315406 T ES 2111717 T GR 3025769 T HK 1004773 A JP 2594877 B JP 6211694 A MX 9305230 A US 5520920 A US 5540918 A | 15-12-1997 29-02-1996 03-03-1994 01-03-1994 08-01-1998 19-03-1998 16-03-1998 31-03-1998 04-12-1998 26-03-1997 02-08-1994 28-02-1994 28-05-1996 30-07-1996 |
| WO 9825620 A | 18-06-1998 | AU 4183897 A EP 0941094 A | 03-07-1998 15-09-1999 |